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09/771,357	01/26/2001	Saraswati Sukumar	JHU1630	6079

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EXAMINER

SOUAYA, JEHANNE E

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/771,357	SUKUMAR ET AL.
	Examiner	Art Unit
	Jehanne E Souaya	1634

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 03 January 2003 .

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-37 is/are pending in the application.
4a) Of the above claim(s) 35-37 is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 1-34 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) .
4) Interview Summary (PTO-413) Paper No(s). ____ .
5) Notice of Informal Patent Application (PTO-152)
6) Other:

DETAILED ACTION

Election/Restrictions

1. Claims 35-37 and nucleic acids corresponding to Twist, RARB2, WT1, HOXA5, 14.3.3 sigma, estrogen receptor, and NES-1 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in a reply dated 1/3/2003. No arguments were presented.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The specification is objected to because the drawings contain sequences that are not designated by a sequence identifier either in the drawings or the “Description of the Drawings” section of the specification. 37 CFR 1.821(d) recites:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the “Sequence Listing” in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by “SEQ ID NO:” in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Either the drawings or the description of the drawings should set forth the proper sequence identifiers for each sequence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing breast cancer or DCIS in a subject comprising obtaining nucleic acid from a blood, plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes, or bone marrow specimen of a subject, and determining the state of methylation CpG islands of the promoter of cyclin D2 nucleic acid, wherein hypermethylation of CpG islands in the promoter of Cyclin D2 is indicative of breast cancer in the subject, does not reasonably provide enablement for a method of diagnosing any cellular proliferative disorder of breast tissue in a subject comprising determining the state of methylation of one or more nucleic acids isolated from the subject, wherein the state of methylation of one or more nucleic acids as compared with the state of methylation of one or more nucleic acids from a subject not having the cellular proliferative disorder of breast tissue is indicative of a cellular proliferative disorder of breast tissue, a method of diagnosing any cellular proliferative disorder of breast tissue by determining the state of methylation of any region of a cyclin D2 nucleic acid as compared to the state of methylation of cyclin D2 from a subject not having a cellular proliferative disorder of breast tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to detecting any cellular proliferative disorder of breast tissue in any subject by detecting methylation of any region of any nucleic acid as compared with the state of methylation of any nucleic acids from a subject not having the cellular proliferative disorder of the breast. The claims are further drawn to the embodiment wherein the nucleic acid is cyclin D2, and methylation is in any region of cyclin D2. The claims are also broadly drawn to nucleic acids from any sample. The specification, however, does not enable the skilled artisan to make or use the invention commensurate in scope with the claims. Although some claims are of a more limited scope, they are still too broad such that the specification does not enable the broad scope of the claims.

The specification teaches that SAGE analysis revealed that cyclin D2 expression was lower in a small panel of primary breast tumors as compared to immortal human mammary epithelial cell lines (HMEC's) (see p. 35). The specification teaches that 6 of 10 primary breast tumors showed hypermethylation of CpG islands of the cyclin D2 promoter, and that the promoter of cyclin D2 was unmethylated in normal breast epithelial cells. The specification teaches that hypermethylation of the cyclin D2 promoter was also found in 44% of Ductal carcinoma in situ (DCIS) samples. While such teachings establish an association between hypermethylation of CpG islands of the promoter of cyclin D2 and breast cancer and DCIS in patients, the specification has not established an association between methylation of any region or any CG region of cyclin D2 or any nucleic acid and breast cancer, of hypermethylation of the

cyclin D2 promoter or a methylation of any nucleic acid and any cellular proliferative disorder of breast tissue, or diagnosis from nucleic acids from any sample. The specification does not enable the full scope of the broadly claimed invention.

The claims are broadly drawn to a method of diagnosing any cellular proliferative disorder of breast tissue in a subject comprising determining the state of methylation of one or more nucleic acids isolated from the subject, wherein the state of methylation of one or more nucleic acids as compared with the state of methylation of one or more nucleic acids from a subject not having the cellular proliferative disorder of breast tissue is indicative of a cellular proliferative disorder of breast tissue. It is noted that the claims do not set forth the relationship between the nucleic acids of a subject and that of a control subject. Such claims merely set forth an invitation to experiment as they leave it up to the skilled artisan to determine if an increase or decrease in methylation of a nucleic acid compared to methylation in a control subject is indicative of a cellular proliferative disorder of the breast. While hypermethylation of CpG islands of promoters of some genes involved in cancer have been associated with breast cancer, the specification has not set forth any predictable correlation that hypomethylation of any nucleic acid is indicative of breast cancer. Further, the claims merely require a comparison between nucleic acids between two individuals, one of which does not have a cellular proliferative disorder. (The claims do not require that the nucleic acids be the same). Such analysis yields unpredictable results. For example, Lehman et al (American Journal of Pathology, vol. 160, 2002; pp 605 – 612) teaches analysis of promoter methylation of different tissue samples in different nucleic acids. With regard to 14.3.3 sigma (see Figure 3), it is apparent that merely comparing methylation status of the promoter in two different individuals will not establish a

predictable association to diagnosis of breast cancer. For example, the 14.3.3 sigma promoter is very heavily hypermethylated in normal lymph node (it is noted that such is a sample from a healthy donor) whereas normal breast epithelial cells are significantly less methylated. The skilled artisan would not be able to establish a predictable correlation between such significant changes in methylation status and breast cancer as the analysis from lymph node was from a healthy donor. Further, diagnosis of DCIS or breast cancer based on a difference in methylation status for *any* specimens would not be predictably correlative of disease using 14.3.3 sigma because the methylation status of the promoter is the same or similar in DCIS or hyperplasia and normal lymph (such is also true for normal blood samples, see p.608, col. 1, 2nd full para). Further, the methylation status in normal breast epithelial cells and papiloma are also very similar. In addition, Lehman specifically teaches that such data excludes the use of the detection of 14.3.3 sigma hypermethylation in lymph nodes or peripheral blood for the screening for circulation tumor cells or micrometastasis that would otherwise be promising. Additionally, the claims require that a comparison of methylation status of any nucleic acid from any specimen will be indicative of any cellular proliferative breast disorder. However, the specification has not established that methylation status as compared to normal subjects, of the promoter of any nucleic acid from a sample taken from liver, for example, will be indicative of a cellular proliferative disorder of the *breast*, as opposed to a cellular proliferative disorder of the liver. The specification provides no evidence of a predictable correlation between diagnosis of breast cancer and hypermethylation or hypomethylation of any nucleic acid taken from a liver sample. The art demonstrates that hypermethylation of the promoter region of a number of different genes has been correlated to a number of different cancers. For example, GSTP1 promoter

hypermethylation has been associated with prostate, renal, and breast cancer (see Esteller et al; Cancer Research, vol. 58, pp 4515-4518; 1998). However, Esteller does not teach, and the skilled artisan would not conclude based on the teachings of Esteller, that detection of GSTP1 hypermethylation in a prostatic sample would be indicative of renal cancer. Based on the lack of guidance in the specification and the unpredictability taught in the art with regard to an association between methylation status of any nucleic acid from any specimen and cellular proliferative disorders of the breast, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed.

The claims are further drawn to a method of detecting any cellular proliferative disorder of the breast by comparing methylation of cyclin D2 nucleic acid. The specification teaches that 'cellular proliferative disorder' could be a benign or malignant neoplasm, however the specification does not limit the definition to such. The only aberrant breast tissue specimens that were analyzed however were primary breast tumor tissue and DCIS (preneoplasia). While the specification teaches that cyclin D2 promoter was hypermethylated in such specimens, as compared to no detectable methylation in normal epithelial cells, such teaching does not establish a predictable correlation that any cellular proliferative disorder could be diagnosed by a comparison of cyclin D2 or any nucleic acid's methylation status. In addition, the art demonstrates the unpredictability with regard to cyclin D2 hypermethylation and cellular proliferative disorders. Lehman teaches that aberrant methylation of cyclin D2 was restricted to cancerous epithelium. Lehman teaches no appreciable difference in methylation status between normal lymph or breast epithelial samples and either hyperplasia or papilloma. This is in contrast to methylation status of RASSF1A, wherein aberrant methylation was found in

hyperplasia, papilloma, and DCIS as compared to normal lymph and epithelial samples. Therefore, Lehman teaches that while aberrant methylation of certain genes is indicative of DCIS, such a correlation cannot be predictably made with regard to any cellular proliferative disorder of the breast. Trial and error analysis would be required of the skilled artisan to determine whether a correlation exists between methylation status and any cellular proliferative disorder of the breast for any gene, including cyclin D2. The teachings of the art demonstrate that such analysis is unpredictability. Accordingly, due to the lack of guidance from the specification as to predictable correlation between methylation status and any cellular proliferative disorder of the breast in any gene, including cyclin D2, and the unpredictability taught in the art with regard to establishing such a correlation, such analysis is considered undue.

The claims are further drawn to a method of detecting any cellular proliferative disorder of the breast by comparing methylation of any region of any nucleic acid, or more specifically, cyclin D2 nucleic acid. The specification teaches, and the art supports, that hypermethylation of CpG islands in the promoter region of cyclin D2 is associated with DCIS. Further, the art teaches that extent of hypermethylation in the promoter region of cyclin D2 is associated with histological grade of tumors. However, neither the specification nor the art provide a predictable correlation between hypermethylation in any region of any nucleic acid and any cellular proliferative disorder, including breast proliferative disorders, or cyclin D2 nucleic acid and cellular proliferative disorders of the breast. The specification teaches that in somatic cells, 80% of CGs are methylated, while CpG islands, which are present in more than 60% of human genes are normally unmethylated. The specification provides no comparison of normally methylated CGs in normal samples vs breast cancer or DCIS samples to establish a predictable correlation

between methylation status in any region of any nucleic acid or cyclin D2 and any cellular proliferative disorder of the breast. Further, the specification teaches that hypermethylation of the promoter leads to cyclin D2 gene silencing in a number of different primary tumors tested. There is no teaching or guidance in the specification, however, that hypermethylation in an intron or exon, for example, of cyclin D2 would lead to decreased expression of cyclin D2 or be associated with breast cancer or any cellular proliferative disorder of the breast. Undue experimentation would be required of the skilled artisan to practice the invention as broadly as is claimed. The skilled artisan would have to screen a large number of breast tumor samples and normal hepatocytes, and using trial and error analysis, would have determine the level of methylation of CpG dinucleotides in all regions of the gene encoding cyclin D2 to determine whether hypermethylation in any region of the gene is associated with breast cancer or any cellular proliferative disorder of breast tissue. Such analysis would require trial and error, the outcome of which is unpredictable, thus constituting undue experimentation.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 25-27, 30, 33, and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Ferguson et al (PNAS, vol. 97, pp 6049-6054; May 2000).

Ferguson et al teach that hypermethylation of the sigma promoter is largely responsible for silencing of the sigma gene and occurs in a majority of breast cancers. Ferguson et al teach a method wherein the state of methylation of CpG rich region of the 14.3.3 sigma gene promoter was determined using methylation specific PCR in samples of breast tumor (claims 33 and 34) from a subject and compared to the methylation status of the 14.3.3 sigma promoter in normal breast tissue (claims 1, 25-27; see abstract, p. 6050, table 1, p. 6054, col. 2). Ferguson et al specifically teach sense and antisense primers for use in the method (p. 6050, col. 2) (claim 30).

8. Claims 1, 25-27, 30, 33, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Esteller et al (Cancer Research, vol. 58, pp 4515-4518).

Esteller et al teach a wherein the state of methylation of CpG rich region of the GSTP1 gene promoter was determined using methylation specific PCR in samples of breast tumor (claims 33 and 34) from a subject and compared to the methylation status of the GSTP1 promoter in normal breast (claims 1, 25-27; see abstract, p. 4515, col. 2, table 1, Figure 1A). Esteller et al specifically teach sense and antisense primers for use in the method (p. 4515 col. 2) (claim 30).

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Patent examiner

Art Unit 1634

Jehanne Souaya
5/1/03